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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,888	09/27/2005	David James Paterson	P-7945-US	8757

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PEARL COHEN ZEDEK, LLP
1500 BROADWAY 12TH FLOOR
NEW YORK, NY 10036

EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/534,888	PATERSON, DAVID JAMES	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims **1-19** are pending and presently under examination with respect to elected invention.

Specification

Foreign priority date for the invention, applied under 35 USC 119 (a)-(d) for the application number United Kingdom 02264638 dated 11/13/2002 is granted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims **1-19** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention.

The above claims are directed to a method of treating a patient by delivering a nucleic acid molecule that increases the expression of nitric oxide synthase (NOS) into cardiac autonomic structures and to a pharmaceutical composition comprising nucleic acid molecules, when expressed in cardiac autonomic structures increases nitric oxide synthase level.

The scope of the invention as claimed encompasses the use of any nucleic acid molecule that is capable of increasing any NOS in order to treat any disease comprising a step of delivering by any route to any site on cardiac autonomic structure and further encompasses a pharmaceutical composition comprising any nucleic acids for the same. The description of invention in the as filed application however, does not provide support for the full scope and breadth of the claims or to even a substantial part of the same.

The specification only provides guidance and/or evidences regarding use of a NOS-1 gene in a Adenoviral vector (Ad-NOS) for gene transfer into atrial walls by direct injection in guinea pig and spontaneously hypertensive rat (SHR) model to obtain an over expression of NOS-1 protein and the increased the vagal responsiveness relative to controls.

Besides NOS-1 gene in Adenovirus virus vector in virus particle, the specification fails to disclose any other nucleic acid molecule that is capable of in creasing the levels of NOS as broadly claimed. Further it does not disclose as specific examples the use of naked DNA or non-viral vector packaging, or direct delivery into vagus nerve or the use of a construct with non-constitutive promoter or a promoter that is specifically active in cholinergic ganglia, or cardiac delivery of nucleic acids with micro-bubbles that can be disrupted by ultrasound.

Given the paucity in the art regarding the claimed method of injection into vagus ganglion for a tissue specific expression NOS-1 transgene to treat a heart ailment it is incumbent upon the applicant to provide enabled descriptions of the claimed nucleic acid molecules and methods and sufficient number of examples to support the full breadth and scope of the claims. In the absence of adequate description commensurate with the scope and the breadth of the claims one of ordinary skill in the art would conclude that the inventor(s), at the time the application was filed, was not in possession of the broadly claimed invention. Claiming all divergent species that achieve a result as contemplated by the application without defining the means and/or uses will do so not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. "The written description requirement has several policy objectives. The essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998)."

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention as claimed is "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention (January 5, 2001 Fed.Reg., Vo.66, No. 4, pp. 1099-11).

At the best the specification teaches an adenovirus vector with NOS-I gene which when injected into guinea pig atrial wall or a rat over-expresses NOS-I protein that co-localizes to cholinergic ganglion and causes an increase in vagal toning and decrease in heart rate. Further it teaches a pharmaceutical composition comprising adenoviral vector with coding sequences for NOS-I gene operably linked to a promoter. Besides NOS-1 gene, the specification fails to disclose any other nucleic acid molecule that is capable of in creasing the levels of NOS as broadly claimed.

Claims 1, 3-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using an adenovirus vector encoding NOS-I gene which when injected into atrial wall of a rodent increases NOS-I protein expression levels and cause an increase in vagal toning, is not enabled for treating any patient for any and all diseases or disorders by delivering any and all other nucleic acid molecules that may be capable of increasing NOS expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At issue, under the enablement requirement of 35 U.S.C. 112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be

expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through "undue experimentation" in order to practice the invention.

Nature of the invention and the breadth of the claims:

The scope of the invention further encompass treatment of all patients by gene therapy involving a targeted gene delivery of NOS gene to cardiac autonomic structures for treating heart diseases such as sudden cardiac death, arrhythmia, myocardial infraction etc. In the absence of representative number of enabled examples in the specification commensurate with the breadth of the claims one of ordinary skill in the art would conclude that the invention is unpredictable and would require undue experimentation to practice the invention in its full scope. Applicants' attention is drawn to In re Shokal, 242 F.2d 771, 113 USPQ 283 (CCPA 1957). The test is whether the number of claimed species nucleic acid species, sites of delivery and disease treatments completed by applicants prior to the reference date or the date of the activity provided an adequate basis for inferring that the invention has generic applicability. Examiner, having read the instant specification broadly in the light of the Art, finds that such is not the case and hence concludes that the instant application does not reasonably provide enablement for the full breadth and scope of the claims and would have required undue experimentation for a skilled artisan to make and **use** the full scope of the methods as claimed.

The level of one of ordinary skill in the Art at the Time of Invention: The level of one of ordinary skill in the art at the time of filing of the instant application is high requiring an advanced degree or training in the relevant field. The status of the

art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

Guidance of the Specification and the Existence of Working Examples: With respect to invention instant specification however only provides guidance and/or evidences regarding use of an adenovirus vector comprising a NOS-I gene when injected into guinea pig heart atrial wall or a rat over-expresses NOS-I protein which localizes to a cholinergic ganglion and causes an increase in vagal toning and decreased heart rate. Given the state of the art coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the full scope of the methods of treating all heart diseases as claimed.

State of the Art, the Predictability of the Art: At about the effective filing date of the present application art is unpredictable with regard to methods of gene transfers in vivo using both viral and non-viral vectors, as has been claimed in the instant invention, art is still unpredictable with regard to efficacy, specificity and safety. Gene therapy or in vivo gene transfers are still considered to be highly experimental area of research and it has been difficult to predict the out come of many therapeutic genes and vector systems because of various factors that govern the expression, therapeutic potential of the transduced genes, and the undesirable host immune reactions etc., in vivo (Reviewed in Goncalves et al, Bioessays, 2005, 27: 506-517). In addition there exists an unpredictability about the degree to which a foreign gene or vector would interfere with cellular genetic material as observed in treatment of X-SCID patients " These serious adverse events presented as a leukemia-like syndrome were surprising since the risk of insertional oncogenesis was considered to be negligible based on previous trials and on the perceived, though not universally accepted, notion of random retroviral integration" (Goncalves, Bioessays, 2005, 27: 506-517, p. 514, col.2, 1st ¶).

Amount of experimentation necessary: These claims are not enabled because one of skilled in the art would not be able to rely upon the state of the art in order to successfully predict a priori the in vivo effects of claimed gene transfers in a subject. Accordingly, in view of the lack of teachings in the art or guidance provided by

the specification with regard to an enabled use of a method for safe treatment of a disease or conditions of heart and in sufficient number of species as of around the filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. At the best the specification as filed is found only enabled for a method of using an adenovirus vector encoding NOS-I gene which when injected into atrial wall of a rodent increases NOS-I protein expression levels and cause an increase in vagal toning.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, 5, 13-16 are rejected under 35 USC 102 (a) as being anticipated by Kishi et al., (2002, Hypertension 39:264-268).

The above claims are directed to a method of treating a heart disease by gene therapy with nucleic acid molecules, that increase the expression of nitric oxide synthase, delivered to patient's cardiac autonomic structure and a pharmaceutical composition comprising said nucleic acid molecule.

Regarding claims 1-2 and 5 Kishi teaches a composition of method of treating a stroke prone spontaneously hypertensive rats by NOS gene over expression in rostral ventrolateral medulla (RVLM), containing neurons involved in autonomic cardiovascular regulation (p.264, abstract) using a composition of adenoviral vector encoding a operably inserted eNOS (NOS-3) gene and delivered in vivo by a stereotaxic injection in to site such as rostral ventrolateral medulla (p.264, col.1). Kishi further teaches that said gene therapy decreases blood pressure, decreases heart rate and decreases sympathetic nerve activity. Regarding claims 13-16 Adenoviral vector comprises DNA

that is non-replicating and when inside the cell the DNA is non-integrating and episomal in nature. Rejected claims are within the scope Kishis disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 7, 9-11 13-19 are rejected under 35 USC 103 (a) as being unpatentable over Kishi et al., (2002, Hypertension 39:264-268), as applied to claims 1-3, 5, 13-16 as above in view of YI-FAN et al (2002, Am. J. Heart. Circ. Physiol. 282:H594-H601), Lonnerberg et al (1995, Proc.Natl. Acad Sci. USA 92: 4046-4050), Edelberg et al (2001, Heart 86:559-562).

The above claims are directed to a method of treating a heart disease by gene therapy with nucleic acid molecules, that increase the expression of nitric oxide synthase, delivered to patient's cardiac autonomic structure and a pharmaceutical composition comprising said nucleic acid molecule.

Regarding claims 1-2 and 5 Kishi teaches a composition of method of treating a stroke prone spontaneously hypertensive rats by NOS gene over expression in rostral ventrolateral medulla (RVLM), containing neurons involved in autonomic cardiovascular regulation (p.264, abstract) using a composition of adenoviral vector encoding a operably inserted eNOS (NOS-3) gene and delivered in vivo by a stereotaxic injection in to site such as rostral ventrolateral medulla (p.264, col.1). Kishi further teaches that said gene therapy decreases blood pressure, decreases heart rate and decreases sympathetic nerve activity. Regarding claims 13-16 Adenoviral vector comprises DNA that is non-replicating and when inside the cell the DNA is non-integrating and episomal in nature. Kishi however, does not teach specific delivery of NOS gene into vagus

nerve or use of a cholinergic ganglia tissue specific promoter or NOS-1 gene delivery, or non-viral genetherapy vector and delivery in to the heart.

YI-Fan teaches regarding limitations of claim 6 of in vivo gene transfer of NOS-1 (nNOS) gene into paraventricular nucleus (p.H594, abstract and p.H596, col.2, 2nd paragraph).

Lonnerberg teaches regarding limitations of claims 9 and 18-19 of cholinergic specific promoter methods of construction and use in the expression of reporter gene and tissue-specific expression in transgenic mice (p.4046, Abstract and p.4048, col.1, Table 1).

Edelberg teaches regarding limitations of claims 7, 10-11 and13-16 gene delivery by recombinant vectors containing naked DNA and gene expression by myocardial injection into right atrium of a pig heart to modulate hear rate (p.559, abstract and p.560, col.1, 3rd paragraph)

Thus it would have been obvious for one of ordinary skill in the art to incorporate into compositions of gene constructs of viral or non viral vectors NOS-1 gene and non constitutive promoters that expresses specifically cholinergic ganglia use a method of targeting said nucleic acids to cardiac tissue, nerve or right atrial tissue for over expression of NOS to treat an experimental animal for heart disease. One skilled in the art would be motivated to do so for treating aheart disease because of the teachings of Kishi's, Yi-Fan's, Lonnerberg's and Edelberg's teachings as above.

Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier

communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Dave Nguyen*, may be reached at **(571) 272-0731.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

Kelaginamane T. Hiriyanna

Patent Examiner

Art Unit 1633

SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER

3/20/06